

REMARKS

These remarks are in response to the Office Action mailed March 5, 2010. Claims 64 and 106 have been cancelled without prejudice to Applicants' right to prosecute the cancelled subject matter in any divisional, continuation, continuation-in-part or other application.

Applicants respectfully thank Examiner Dunston for the courteous telephonic interview conducted with Applicants' representative, Joseph R. Baker, Jr., on March 24, 2010. During the Interview amendments and remarks were considered to overcome the pending rejections.

Claim 49 and 98 has been amended as suggested by the Examiner during the telephonic interview to overcome the pending rejection. Support for the amendments can be found in paragraphs [0027] and [0032] wherein the specification describes the use of measuring histologically normal mucosa. Applicants respectfully request rejoinder of claim 50 and 99 which are set forth in proper dependent format.

No new matter is believed to have been introduced.

I. CLAIM OBJECTIONS

Claim 49 and 98 are objected to for misplacement of the word "and". Applicants have amended the claims to place the word "and" in an appropriate position of the claim. The objection may be withdrawn.

Claims 50 and 99 stands objected to as allegedly directed to a non-elected invention. Applicants respectfully request rejoinder of claim 99 and claim 50, both of which are in proper dependent format.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 98-106 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 98 is allegedly vague and indefinite because the preamble and the last "wherein" clause are inconsistent.

Applicants have amended claim 98, upon which claims 99-106 depend, to recite "indicative of an increased risk of colorectal cancer". Applicants believe that

this amendment overcomes the rejection. Accordingly, Applicants request withdrawal of the rejection.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 98-106 stand rejected under 35 U.S.C. §112, first paragraph, because, while being enabling for a method where an increase in expression of at least SEQ ID NO:1 and/or 2 is indicative of an "increased risk" of colorectal cancer, the claims are allegedly not enabled for a method of "diagnosing" colorectal cancer. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the invention is enabled with respect to diagnosis, however, the rejection is moot following the amendments set forth above to address the §112, second paragraph rejection. Applicants have amended claim 98, upon which claims 99-106 depend, to recite "indicative of an increased risk of colorectal cancer". Applicants believe that this amendment further address this rejection.

IV. REJECTION UNDER 35 U.S.C. §103

Claims 49, 54-55, 57, 61, 63, 64, 96, 98, 100-103, 105-106 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over a plurality of references in combination (*e.g.*, Kanaoka *et al.*, in view of GenBank Accession No. XM-051900, Brew *et al.*, di Celle *et al.*, and GenBank Accession No. XM_031289). Applicants respectfully traverse this rejection.

It is important to note that the Patent Office has spent a great deal of effort in addressing the fact that determining a risk of colorectal cancer is different than diagnosing colorectal cancer. In particular, Applicants direct the Examiner to pages 5-14 of the present office action wherein the Patent Office repeatedly takes the position that diagnosis (*i.e.*, the presence of cancer cells) is different than determining a risk of cancer and one is not predictive of the other. In other words, the Patent Office has taken the clear position that diagnosing and determining a risk of colorectal cancer provide far different enablement requirements. With this in mind, Applicants respectfully submit that the teaching of the primary reference, Kanaoka *et al.*, and the secondary reference, Brew *et al.*, are not enabled for

determining a risk of a colorectal cancer or polyps. In order for a reference to be properly used under 35 U.S.C. §§102 and 103, the disclosure of the reference must enable the claimed invention.

More particularly, the references, in any combination, do not teach or suggest obtaining a biological sample from normal appearing mucosa. Both Kanaoka *et al.* and Brew *et al.*, obtain cancer cell samples. It will be readily apparent to the Examiner that cancer cells are not "normal". Thus, the references do not teach or suggest each and every element of Applicants' claimed invention.

Turning to the primary reference, Kanaoka *et al.*, the reference teaches measuring CEA and COX2 in patients that have been previously diagnosed with colorectal cancer using colonoscopy and blood-fecal measurements. In Kanaoka *et al.*, the expression of COX-2 is measured from existing cancer cells not "normal" cells as set forth in Applicants' claimed invention. The Patent Office misstates the teachings of Kanaoka *et al.* at page 16, lines 7-8, when the Patent Office states, "...wherein an increase in COX-2 expression correlates with an increased risk of colorectal cancer. . . ." (emphasis ours). This teaching is not found in Kanaoka *et al.* Rather Kanaoka *et al.* do not teach or suggest measuring a "risk" but rather that COX2 is increased in subject "having" colorectal cancer from cancer cell samples. Furthermore, there is no mention of polyps in Kanaoka *et al.* (see, Applicants' claim 49).

The Patent Office admittedly states that Kanaoka *et al.* does not teach or suggest a COX-2 sequence, labeling of cDNA with a chromophore or the use of IL-8 or a sequence for IL-8. To overcome these latter deficiencies the office combines Gen Bank Accession No. XM_051900, Brew *et al.*, GenBank Accession No. XM_031289 and DiCelle *et al.* However, Applicants respectfully submit that even in view of the additional references, the combination fails to teach or suggest determining a risk for colorectal cancer.

Turning to Brew *et al.*, Brew *et al.* is similar in teaching to Kanaoka *et al.* except Brew *et al.* utilizes IL-8. Again, as with Kanaoka *et al.*, Brew *et al.* is not determining a risk of colorectal cancer, but rather is simply measuring expression in existing tumors (*i.e.*, known and identified colorectal cancers). Accordingly, as with Kanaoka *et al.* the combination of Kanaoka *et al.* and Brew *et al.* fails to teach or

suggest determining a risk of colorectal cancer based upon an expression profile of a biomarker panel comprising IL-8 and COX-2.

Again, as the Patent Office is keen to point out, there can be no predictability that measuring an expression level in cancer cells translates to a method of assessing a risk of cancer. As the Examiner will recognize, the combination of IL-8 and COX-2 is not taught or suggested by the references when combined and the combination of references do not teach or suggest a method of assessing a risk of colorectal cancer or polyps. It was not until the inventors performed the research and provided the present invention that one of skill in the art could have predicted that IL-8 and COX-2 as well as in combination with other markers disclosed in the present specification that a risk of colon cancer could be predicted based upon an expression profile.

To suggest that measuring IL-8 or measuring COX-2 in existing tumor cells in, for example, a culture environment demonstrates an effective diagnostic for predicting a risk of cancer based upon normal appearing mucosa violates basic fundamental science principles. More importantly, the suggestion that measuring, for example, COX-2 (as described by Kanaoka *et al.*) enables the world to develop a biomarker panel for 'predicting or assessing a risk of cancer' from normal appearing mucosa violates the enablement requirement so duly noted in the pending office action.

The addition of, DuBois *et al.*, Park *et al.*, and GenBank Accession No. XM_003059, to the prior reference to allegedly generate a prima facie case of obviousness against claims 50-51 and 99 fail to overcome the deficiencies of the prior 5 references. Accordingly, the combination of all eight (8) references still lacks any teaching or suggestion of determining a risk of colorectal cancer and more importantly, the combination fails to provide enablement or a reasonable expectation of success when combined.

Claims 52 and 53 stand rejected as allegedly obvious over no less than ten (10) references in combination. The addition of, Baker *et al.* and Gould *et al.*, to the prior 8 references to allegedly generate a prima facie case of obviousness against

claims 52-53 fail to overcome the deficiencies of the prior 8 references. Accordingly, the combination of all ten (10) references still lacks any teaching or suggestion of determining a risk of colorectal cancer and more importantly, the combination fails to provide enablement or a reasonable expectation of success when combined.

Claims 49, 54-55, 57, 96, 98 and 100-102 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Hao *et al.*, in view of GenBank Accession No. XM_051900, in view of Brew *et al.*, in view of DiCelle *et al.*, and in view of GenBank Accession No. XM_031289. Applicants respectfully traverse this rejection.

As with Kanaoka *et al.* and Brew *et al.*, the Hao *et al.* reference identified COX-2 expression in existing cancer cells. Thus, there is no predicting a "risk of a cancer" described, taught or suggested in this reference. Furthermore, the mere existence of COX-2 in cancer cells is insufficient to place Applicants' invention into the public domain. Applicants have identified a combination of biomarkers that provides selectivity and specificity in determining a risk of colorectal cancer. As with Kanaoka *et al.*, Hao *et al.* do not teach or suggest the COX-2 sequence, amplification and quantification and measurement of IL-8.

The addition of the secondary references to Hao *et al.* do not overcome the deficiencies including, for example, determining a risk of a cancer in a subject.

Claims 50-51 and 99 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over no less than eight (8) references (Hao *et al.*, GenBank Accession No. XM_051900, Brew *et al.*, DiCelle *et al.*, GenBank Accession No. XM_031289, DuBois *et al.*, Park *et al.*, and GenBank Accession No. XM_003059). Applicants respectfully traverse this rejection.

As with the rejections above, the combination of references fail to teach or suggest assessing a risk of colorectal cancer. Hao *et al.* and Brew *et al.* were addressed above. The addition of DuBois *et al.*, Pak *et al.* and GenBank Accession No. XM_003059, fails to overcome the deficiencies of the references as discussed above.

Claims 52 and 53 stand rejected as allegedly obvious over no less than ten (10) references. The previous 8 references were addressed above. The addition of Baker *et al.* and Gould *et al.* do not overcome the deficiencies of the primary references.

Claims 61-62 and 103-104 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over no less than seven (7) references (*i.e.*, Hao *et al.*, GenBank Accession No. XM_051900, Brew *et al.*, DiCelle *et al.*, GenBank Accession NO. XM_031289, Melville *et al.*, and Ristimaki *et al.*). Applicants respectfully traverse this rejection.

The addition of Melville *et al.* and Ristimaki *et al.* do not overcome the deficiencies set forth for the combination of Hao *et al.*, Brew *et al.*, DiCelle *et al.*, and the GenBank references.

Claims 61, 63, 64, 103 and 105-106 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over no less than six (6) references (*i.e.*, Hao *et al.*, GenBank Accession No. XM_051900, Brew *et al.*, DiCelle *et al.*, GenBank Accession NO. XM_031289, and Davidson *et al.*). Applicants respectfully traverse this rejection.

The addition of Davidson *et al.* do not overcome the deficiencies set forth for the combination of Hao *et al.*, Brew *et al.*, DiCelle *et al.*, and the GenBank references.

Simply put the Patent Office has combined no less than 6 references to allegedly arrive at Applicants' invention. This, in itself, demonstrates the non-obviousness of Applicants' claimed invention. It is readily apparent from the references that none of the reference alone or in combination teach or suggest compositions or methods for predicting a risk or "assessing a risk for colorectal cancer" by sampling normal appearing mucosa. The Patent Office has spent a great deal of effort and time in the present office action and the prior office actions to point out the complicated nature of the present invention and has on numerous occasions stated that Applicants' invention lacks enablement and is unpredictable. Yet the Patent Office then takes the position that the references cited herein (e.g., Kanaoka

et al. and Brew et al.), lacking any data related to predicting cancer and lacking any data related to the biomarkers used in the present invention, are enabling. In contrast, Applicants have provided clinical data experimentation to further prove the effectiveness of the claimed invention. Thus, it is clear that in the absence of that same standard applied to enable Applicants' invention, the references cited by the Office, alone or when combined, cannot possibly be enabled to allow any predictability of success leading to Applicants' claimed invention.

For at least the foregoing reasons, Applicants respectfully submit that the combination of the references fail to set forth a prima facie case of obviousness for at least two fundamental reasons: (1) there is no predictability of success when the references are combined and (2) the combination fails to teach or suggest each and every element of Applicants' claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the pending claims.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,
GAVRILOVICH, DODD & LINDSEY LLP

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By: /Joseph R. Baker, Jr./
Joseph R. Baker, Jr.
Registration No. 40,900

4660 La Jolla Village Drive, Suite 750
San Diego, California 92122
(858) 458-3607